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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,906	02/26/2001	Hans-Dieter Flad	661-50303	3318

20736 7590 07/03/2003

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	18

DATE MAILED: 07/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

F/G

Office Action Summary	Application No.	Applicant(s)	
	09/700,906	FLAD ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 14-84* is/are pending in the application.

4a) Of the above claim(s) *47,48,52,53,76,80 and 81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 14-46, 49-51, 54-75, 77-79, 82-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *47,48,52,53,76,80 and 81* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed April 8, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed December 18, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. Applicant is advised that claim 15 was not indicated as allowable as asserted by applicant; in fact, said claim was only indicated as allowable if the claim from which it depended were to overcome the pending rejection under 35 U.S.C. § 112 2nd paragraph. Furthermore, it is noted that applicant's claims were not rejected over prior art due to the significant issues related to 35 U.S.C. § 112 2nd paragraph, which prevented the claims from being fully examined; however, related art was cited to inform applicant of the existence of potential prior art.

2. The indicated allowability of claim 15 is withdrawn in view of the newly discovered reference(s) to the claimed SEQ ID NO: 3. Rejections based on the newly cited reference(s) follow.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

4. Newly submitted claims 47, 48, 52, 53, 76, 80 and 81 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims

47, 48 and 76 are drawn to specific nucleobase regions, nucleobases regions 197-2673 in claims 47, and nucleobases 197-2673 in claims 48 and 76 of the instant target transcript, that have not been specifically recited in any claim to date. While SEQ ID NO: 1, which is generic to the newly claimed subsequences above, and subsequence 197-9962 have been searched, the specific subsequences of 197-2673 and 197-2673 have not been specifically searched, as they have not been specifically claimed before.

This international searching authority considers that newly added claims 47, 48 and 76 in this international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2, and 13.3) for the reasons indicated below:

According to the guidelines in Section (f)(i)(a) of Annex B of the PCT Administrative Instructions, the special technical feature as defined by PCT Rule 13.2 shall be considered to be met when all the alternatives of a Markush-group are of similar nature. For chemical alternatives, such as the claimed sequences, the Markush group shall be regarded as being of similar nature when

(A) all alternatives have a common property or activity and
(B)(1) a common structure is present, i.e, a significant structure is shared by all of the alternatives or
(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to an art recognized class of compounds in the art to which the invention pertains.

The newly claimed subsequence regions listed in the claims above are considered to be each separate inventions for the following reasons:

The new antisense sequences that target the newly claimed subsequence target regions do not meet the criteria of (A), common property or activity or (B)(2), art recognized class of

compounds. The new antisense sequences that target the newly claimed subsequence target regions are considered to compose a distinct subset of those antisense sequences that targets the overall SEQ ID NO: 1, because antisense sequences that target the overall target may not target the subsequence that is newly claimed. Therefore, the newly claimed antisense sequence do not necessarily function in the same way as those directed to the originally examined sequence (i.e. SEQ ID NO: 1) and subsequence (i.e. the region of the instant target identified as nucleobases 197-9962), in the context of the claimed invention. They further do not necessarily share a common sequence as those antisense sequences encompassed by the original claims. These newly claimed antisense sequences cannot be substituted, one for the other, with the expectation that the same intended result would be achieved. Further, the newly claimed antisense sequences do not meet the criteria of (B)(1), as they do not share, one with another, a common core structure with those of the originally examined invention. In summary, unity of invention between the antisense compounds directed to the originally claimed sequence and the newly claimed regions is lacking, and each sequence claimed is considered to constitute a special technical feature.

5. For the same reasons, unity of invention is considered to be lacking in regards to the newly claimed modifications. Claims 52, 53, 80 and 81 are drawn to nucleotide modifications comprising hexose and propinyl moieties that are distinct from any previously claimed modifications. They do not share a common core and are not an art recognized class of compounds as those originally examined, and newly claimed modifications also behave differently from any previously examined nucleobase modification. Therefore, unity of invention is lacking between these newly claimed modifications and those examined previously.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 47, 48, 52, 53, 76, 80 and 81 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Response to Arguments

6. Claim 9 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of Ki-67 expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of Ki-67 expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the same reasons of record as cited in the Office communication mailed December 18, 2002.

Furthermore, claims 1 and by dependency, all remaining claims, have been amended to recite a method of preparing a medicament for destroying proliferating cells. While the functional language of "medicament" is not given patentable weight in the consideration of prior art, such functional language is given consideration in terms of 35 U.S.C. § 112 1st paragraph enablement and 35 U.S.C. § 112 1st paragraph written description insofar as such language directly implicates the use of the instantly claimed compounds and methods in the treatment of disease states *in vivo*. Accordingly, pending claims 1-8, 10, 16-30, and 43-84, drawn to methods of making and using antisense compounds as medicaments for use *in vivo*, are newly rejected for

the same reasons of record as cited in the Office communication mailed December 18, 2002. The rejection of the previous Office action as it relates to these claims is stated towards the end of this action; however, arguments that may pertain both to rejection of record and to the rejection as it is newly applied follow directly below.

Applicant has traversed the rejection above on the grounds arguing that the four main sources of unpredictability that were cited in the previous Office action don't apply to applicant's instant invention. Applicant has further submitted a 132 declaration that applicant alleges provides enablement for the *in vivo* use of oligonucleotides in the treatment of disease.

Applicants' declaration is not convincing, because key factual evidence has not been made available in the declaration that is necessary for providing sufficient guidance to one of skill in the art attempting to practice applicants invention as claimed. For example, as applicants admit in their arguments, one of the key issues in the use of antisense compounds *in vivo* is access of such compounds to unfolded sites within the target mRNA transcript. However, applicants have not disclosed the sequence of any antisense oligo that was used in the experiments of the declaration. In the specification, applicants have disclosed the use of SEQ ID NO: 3 *in vitro*, but applicants have not indicated if this was the sequence used in the declaration. In the absence of knowledge regarding the sequence, it is impossible to tell if the steps and compounds used by applicant in the declaration are those disclosed in the specification as filed. Furthermore, no information at all is provided about the control used. In the absence of this information, the declaration is not considered to support the arguement of enablement for the methods and compounds claimed by applicant.

Furthermore, applicants' arguments regarding the enablement of the instant compounds and methods are not convincing. Specifically, applicants argue that delivery of the antisense oligos to the target cells and cellular uptake is not difficult, because applicants assert that it is well known that oligonucleotides accumulate in the kidney, liver, and in cancerous tissue, and furthermore, applicants assert that it is well-known that these oligonucleotides are available intracellularly.

This is not considered convincing, because applicants have provided no evidence to substantiate the assertion that it is well known that oligonucleotides accumulate in the kidney, liver, and importantly, in cancerous tissue. Applicants have done nothing more than allege this to be true. Furthermore, this allegation contradicts the five review articles cited in the previous Office action that discuss unpredictability regarding access to intracellular targets, and is therefore not convincing.

Applicants further argue that the toxicity and immunological problems that were cited as major sources of unpredicatability in the previous Office action are not problematic in the instant situation. Applicants allege that because cancerous tissue accumulates in oligonucleotides "much more than normal tissue, that this will lead to the death of the tumor cells in cancerogeneous tissue only." Applicant has provided no citations or other evidence that might support this claim of such remarkable specificity for the accumulation of antisense oligos in tumorous cells. Applicants further allege that such immunological problems are desirable, because such immunological stimulation "may even support the antitumoral effect of the activation of the target gene."

This argument is purely speculative. Judged from the perspective of the authors of the five cited review articles, such toxicity and immunological problems are problematic issues for anyone attempting to use antisense oligos *in vivo*. In contrast, applicants are of the opinion that widespread and non-specific immune and toxicity effects may somehow confer antitumoral activity. However, applicants have not provided any evidence or cited any references that may support the claim that generalized immune problems may be beneficial in cancer treatment. In fact, applicants appear to acknowledge the speculative nature of their arguments in stating that such an effect "may even support the antitumoral effect of the activation of the target gene". While it may support this effect, it is more likely that it would not, based on a reading of the cited review articles. At the very least, this statement by applicants appear to indicate that such a result would be unpredictable, which is a critical standard in determining whether one of skill in the art would have to engage in trial and error experimentation to make and use the instant compounds and methods over the scope claimed. For these reasons, applicants arguments are unconvincing, and the rejection of the above claims for lacking enablement over the scope claimed is considered appropriate.

7. Claim 14 is rejected under 35 U.S.C. 103(a) as being anticipated by any of Schluter et al., (J. Cell. Biol. (1993) 123(3) 513-522), Maeshima et al. (J. Am. Soc. Nephrology. 1995. 7(10) 2219-2229) or Duchrow et al. (Arch. Imm. Ther. Exp. 1995. 43(2) 117-21), in view of Baracchini et al. (U.S. Patent Number 5,801,154), for the same reasons of record as cited in the Office action mailed December 18, 2002. Furthermore, newly amended claims 1-10 and 15, and newly added claims 16-46, 49-51, 54-63, 65-75, 77-79, and 82-84 are newly rejected for the

same reasons of record as cited in the previous Office action mailed December 18, 2002. The present rejection as it applies to the amended and added claims appears towards the end of this Office action; however, arguments that pertain to the original rejection of claim 14, and as they may pertain to the new rejection necessitated by applicants' amendment are addressed below.

Applicants have traversed the rejection above by stating that there is no motivation to combine the references above to arrive at applicants claimed invention, and that even if the references were combined, that the claimed invention would not be taught or suggested.

Applicants specifically argue that while Maeshima et al. discloses a phosphorothioated oligo that inhibits Ki-67, that Maeshima et al. does not disclose or suggest an oligonucleotide 22-46 nucleobases long as in the instant claim. Applicants further argue that Maeshima et al. does not advocate or disclose destroying cells as applicants claim the instant compound will do.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., destroying cells as opposed to inhibiting the growth of cells) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, applicants' claimed function of cellular destruction resulting from the administration of antinsense to Ki-67 constitutes an intended use, which is not considered to carry patentable weight, particularly in compound claims. See M.P.E.P. § 2114. Moreover, Maeshima was relied upon solely for the teaching of antisense targeted to Ki-67. Thus, applicants arguments that Maeshima is do not teach those elements relied upon by the examiner, that is, antisense targeted to Ki-67, are not convincing.

Applicants further argue that Schluter et al. which teaches an antisense oligo 21 bases long targeted to Ki-67, does not teach an oligo targeted to Ki-67 between 22 and 47 nucleobases long as instantly claimed, and that Schluter does not teach the functional aspects of applicants claimed invention. Applicants are reminded that Schluter et al. was relied upon only to teach antisense targeted to Ki-67. As per above, the functional language of Schluter is not considered relevant to the instant compound claim.

Applicants argue that Duchrow et al. teaches a nucleoantigen recognized by an antibody to Ki-67, and does not teach or disclose oligos that hybribize to Ki-67. Applicants are reminded that Duchrow was relied upon solely for the teaching of the Ki-67 sequence--applicants arguments do not dispute that Duchrow teaches this.

Finally applicants argue that Baracchini et al. teach antisense compounds and methods of inhibiting a different target than Ki-67. Applicants are reminded that Baracchini et al. was relied upon solely for the teaching of antisense compounds and methods that disclose antisense sequences of up to 50 nucleobases as being preferable lengths.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the references individually do not teach applicants claimed invention, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the

test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, supra.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, motivation to make the antisense oligos was expressly provided by either of Maeshima et al. or Schluter et al. Motivation to make oligos of the length specified by applicant is provided by Baracchini et al., who teach that oligos up to 50 bases long are preferred. One of ordinary skill in the art would have had a reasonable expectation of success of making such longer oligos, since the sequence of the target was taught previously by Duchrow et al. For these reasons, the rejection above is maintained.

Claim Objections

8. Claims 1-10, and 14-84 are objected to because of the following informalities: Said claims lack articles and are thus not grammatically correct sentences. For example, claim 1 recites "Method of preparing..." Inserting the letter "A" before the word "method" in this claim would be remedial. Appropriate correction is required. Although this objection was raised in the previous Office action, applicant's amendment and arguments failed to address this issue.

9. Claims 4, 5, 7, 8, and 10 recite methods according to "anyone" of an earlier claim. As defined by The American Heritage® Dictionary of the English Language, Fourth Edition (Copyright © 2000 by Houghton Mifflin Company. Published by Houghton Mifflin Company.), the term "anyone" refers to "any person", which is inappropriate to the claimed subject matter. Separation of "anyone" into "any one" would be remedial. Applicant should review the specification and claims thoroughly for any other instances of this apparent misspelling.

10. Applicant is advised that should claims 2 and 5 be found allowable, claims 47 and 16 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

11. Claim 49 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 49 does not limit claim 7 from which it depends.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 10, 26-30, 43, 44, and 65-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims above are drawn to compounds or methods of preparing said compounds that are "formulated" for treatment of disease, or in the case of claims 43 and 44, are "selected" to provide a medicament for treatment.

The use of the terms formulated and selected are vague and indefinite, because nothing in the claims or the specification provides any structural or manipulative guidance regarding what "formulated" and "selected" actually encompass. One of skill in the art would not be apprised as to the metes and bounds of such terms, since it is not clear specifically how such compounds are to be formulated or selected.

13. Claims 1-8, 10, 16-30, and 43-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of Ki-67 expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of Ki-67 expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As indicated above, claims 1 and by dependency, all remaining claims, have been amended to recite a method of preparing a medicament for destroying proliferating cells. While

the functional language of "medicament" is not given patentable weight in the consideration of prior art, such functional language is given consideration in terms of 35 U.S.C. § 112 1st paragraph enablement and 35 U.S.C. § 112 1st paragraph written description insofar as such language directly implicates the use of the instantly claimed compounds and methods in the treatment of disease states *in vivo*. Accordingly, amended claims 1-8, and 10, and new claims 16-30, and 43-84, drawn to methods of making and using antisense compounds as medicaments for use *in vivo*, are rejected for the same reasons of record as cited in the Office communication mailed December 18, 2002. Arguments that may pertain to the rejection as it is newly applied here are found above in the "Response to arguments" section; the rejection that follows is essentially a re-iteration of that cited in the Office communication mailed December 18, 2002.

The invention of the above claims is drawn to a medicament and a method of making said medicament, wherein it is to be used in the treatment of the whole animal having a condition associated with Ki-67, wherein said compositions are administered to animals such that the expression of Ki-67 is inhibited. The specification teaches a method of using the oligonucleotide that forms the active ingredient of the above claimed medicament to inhibit the expression of Ki-67 in cells *in vitro*. A declaration has been submitted, but is not considered relevant for reasons given above.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general

methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of treatment of the whole animal using antisense-mediated therapy.

A recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify

oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that

obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of Ki-67 expression *in vitro* as being correlative or representative of the successful *in vivo* treatment of any and/or all conditions or diseases suspected of being associated with Ki-67 expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene

in vivo. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant composition as claimed.

Finally, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered, and most importantly, that target sites in appropriate cells and /or tissues harboring Ki-67 expression such that expression is inhibited, that healthy expression is permitted appropriately *in vivo,* and further, that treatment and/or preventive effects are provided for any and/or all diseases or conditions suspected of being associated with Ki-67 expression *in vivo*. Since the specification fails to provide any guidance for the successful treatment or prevention of any and/or all diseases or conditions suspected of being associated with Ki-67 expression in the whole animal, or their tissues or cells, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention over the scope claimed using the methods presented in the specification without engaging in undue trial and error experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-5, 7, 9, 10, 16, 19, 20, 26, 27, 29, 43-46, 49-51, 54-61, 63, 65-74, 77-79, and 82-84 are rejected under 35 U.S.C. 102(b) as being anticipated by Maeshima et al.

The invention of the claims above is drawn to a method of making a medicament, comprising combining an antisense oligoribo- or oligodeoxyribonucleotide or a physiologically acceptable salt thereof, that hybridizes with the mRNA which codes for the protein Ki-67 with a carrier to prepare a medicament for destroying proliferating cells, and to the oligo or medicament itself, wherein the antisense oligo is complementary to SEQ ID NO: 1, or nucleobases 197 to 9962 of SEQ ID NO: 1, or wherein said antisense is 12 to 66, or 17 to 46 nucleobases long, or wherein one phosphate has been modified, or wherein the medicament is formulated or selected for specific disease treatments.

Maeshima et al. teach a method of making a composition comprising combining an antisense oligoribo- or oligodeoxyribonucleotide that hybridizes with the mRNA which codes for the protein Ki-67 with a carrier and an antisense oligo itself, wherein the antisense oligo is complementary to SEQ ID NO: 1, to nucleobases 197 to 9962 of SEQ ID NO: 1, and wherein said antisense is 12 to 66, or 17 to 46 nucleobases long, and wherein one phosphate has been modified.

15. Claims 1-5, 9, 10, 16, 26, 27, 43-46, 54-61, 65-74, and 82-84 are rejected under 35 U.S.C. 102(b) as being anticipated by Maeshima et al.

The invention of the claims above is drawn to a method of making a medicament, comprising combining an antisense oligoribo- or oligodeoxyribonucleotide or a physiologically acceptable salt thereof, that hybridizes with the mRNA which codes for the protein Ki-67 with a

carrier to prepare a medicament for destroying proliferating cells, and to the oligo or medicament itself, wherein the antisense oligo is complementary to SEQ ID NO: 1, or nucleobases 197 to 9962 of SEQ ID NO: 1, or wherein said antisense is 12 to 66, or 17 to 46 nucleobases long, or wherein the medicament is formulated or selected for specific disease treatments.

Maeshima et al. teach a method of making a composition comprising combining an antisense oligoribo- or oligodeoxyribonucleotide that hybridizes with the mRNA which codes for the protein Ki-67 with a carrier and an antisense oligo itself, wherein the antisense oligo is complementary to SEQ ID NO: 1, to nucleobases 197 to 9962 of SEQ ID NO: 1, and wherein said antisense is 12 to 66, or 17 to 46 nucleobases long.

Claim Rejections - 35 USC § 103

16. Newly amended claims 1-10, and newly added claims 16-46, 49-51, 54-63, 65-75, 77-79, and 82-84 are rejected under 35 U.S.C. 103(a) as being anticipated by either of Schluter et al., (J. Cell. Biol. (1993) 123(3) 513-522) or Maeshima et al. (J. Am. Soc. Nephrology. 1995. 7(10) 2219-2229) in combination with Duchrow et al. (Arch. Imm. Ther. Exp. 1995. 43(2) 117-21), and Baracchini et al. (U.S. Patent Number 5,801,154), for the same reasons of record as cited in the Office action mailed December 18, 2002. This rejection is similar to the rejection of record in regards to claim 14 as described above. Applicants amended and added claims necessitated this

new rejection. Arguments that were directed towards the original rejection of claim 14 but that may pertain to this rejection are addressed above.

The invention of the claims above is drawn to a method of making a medicament, comprising combining an antisense oligoribo- or oligodeoxyribonucleotide or a physiologically acceptable salt thereof, that hybridizes with the mRNA which codes for the protein Ki-67 with a carrier to prepare a medicament for destroying proliferating cells, and to the oligo or medicament itself, wherein the antisense oligo is complementary to SEQ ID NO: 1, or nucleobases 197 to 9962 of SEQ ID NO: 1, or wherein said antisense is 12 to 66, or 17 to 46 nucleobases long, or is SEQ ID NO: 3, or wherein one phosphate has been modified, or has a 3'-3' or 5'-5' internucleotide linkage, or wherein the medicament is formulated or selected for specific disease treatments.

As indicated above, and as per M.P.E.P. §§ 2112.01-2114, if the prior art teaches a compound that is identical in structure to the claimed compound, and the only difference from the prior art is that of a claimed function or intended use, that compound is considered to be taught by the prior art. The same is considered to be true in the case of a process; if no manipulative difference can be found between the claim and the prior art except for a function or intended use, that method is considered to be taught by the prior art. While the functional language of "medicament" is considered for the purposes of compliance with 35 U.S.C. § 112 1st paragraph, said functional language is not considered to carry patentable weight in the consideration of prior art because such language amounts to a function or intended use. Accordingly, and the language drawn to "medicament" is therefore not considered in the instant rejection. Therefore, the limitations stipulated by claims 10, 26-30, 43, and 66-71, drawn towards

compounds and methods of making said compounds that are either "medicaments", or are "selected" or "formulated" for use in treating a disease are not considered to carry patentable weight because there is no apparent structural or manipulative step given by such language.

Schluter et al. teach an oligonucleotide 21 bases long that hybridizes with the mRNA that codes for Ki-67, wherein the antisense oligo is complementary to SEQ ID NO: 1, and to nucleobases 197 to 9962 of SEQ ID NO: 1, and comprises 21 of the 23 bases of SEQ ID NO: 3. Schluter et al. also teach a method of making a composition comprising combining an antisense compound targeted to Ki-67 with a carrier. Schluter et al. do not teach the full length of SEQ ID NO: 3, and do not teach phosphate or 3'-3' or 5'-5' modifications of said oligo.

Maeshima et al. teach an oligonucleotide 18 bases long with phosphorothioate modifications that hybridizes with the mRNA that codes for Ki-67, wherein the antisense oligo is complementary to SEQ ID NO: 1, and nucleobases 197 to 9962 of SEQ ID NO: 1 comprises 18 of the 23 bases of SEQ ID NO: 3, wherein one phosphate has been modified. Maeshima et al. also teach a method of making a compound comprising combining an antisense compound targeted to Ki-67 with a carrier. Maeshima et al. do not teach the full length SEQ ID NO: 3, and do not teach 3'-3' or 5'-5' modifications of said oligo.

Duchrow et al. teach the cDNA sequence encoding Ki-67.

Froehler et al. teach phosphate modifications comprising phosphorothioate and 3'-3' or 5'-5' linkages.

It would have been obvious to one of ordinary skill in the art to modify the antisense compounds of Schluter et al. or Maeshima et al. to make a sequence between 22 and 46 nucleotides long targeted to Ki-67, because Schluter et al. teach such a sequence that it 21

nucleotides long, Maeshima et al. teach such a sequence 18 nucleotides long, and because extending these lengths to 22 nucleotides simply constitutes a design choice that does not affect the inhibitory activity so long as the proper complementary sequence, taught by Duchrow et al., is used. Furthermore, it would have been obvious to one of skill in the art to modify the antisense oligos of Maeshima or Schluter to contain 3'-3' or 5'-5' linkages. One would have been motivated to create such compounds because Schluter et al. and Maeshima expressly teach oligos that are antisense to Ki-67 of the claimed lengths and modifications, and since Froehler et al. teach that phosphorothioate modifications of Maeshima et al. provide nuclease resistance, and that 3'-3' or 5'-5' linkages are an alternative choice that also confers resistance to nucleases. Finally, one would have a reasonable expectation of success of making and using such compounds given that Schluter et al. and Maeshima et al. both teach antisense-mediated inhibition of Ki-67, and Froehler et al. teach that 3'-3' or 5'-5' linkage modifications were known in the art at the time of applicants filing, and since the steps required to make such modifications are routinely performed by one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
June 29, 2003